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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,045	10/20/2003	Thomas B. Ottoboni	375430-002t1d1cl	3501
37509	7590	12/04/2006	EXAMINER	
DECHERT LLP			CAPPS, KEVIN J	
P.O. BOX 10004			ART UNIT	
PALO ALTO, CA 94303			PAPER NUMBER	
			1617	

DATE MAILED: 12/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/690,045	OTTOBONI ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Kevin Capps	1617	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-14 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-14 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 20 October 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |  |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>3/12/04</u> . | 6) <input type="checkbox"/> Other: ____  |

## **DETAILED ACTION**

### ***Status of the Claims***

1. Claims 1-14 are pending and examined on the merits herein.

### ***Priority***

2. Applicant's claim of priority to 09/758,988, which is a divisional application of 09/070,474, which is a continuation-in-part of 08/847,153, is acknowledged.

### ***Information Disclosure Statement***

3. The information disclosure statement (IDS) filed on March 12, 2004, is in compliance with the provisions of 37 CFR 1.97. Accordingly, the IDS is being considered by the Examiner.

### ***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

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1. Determining the scope and contents of the prior art.
  2. Ascertaining the differences between the prior art and the claims at issue.
  3. Resolving the level of ordinary skill in the pertinent art.
  4. Considering objective evidence present in the application indicating obviousness or nonobviousness.
6. Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bichon et al. (Applicant-cited reference on IDS: EP 0 458 745) (Also see the corresponding US Patent 5,840,275) in view of Hilmann et al. (US 4,466,442), and further in view of Bernstein et al. (Applicant-cited reference on IDS: WO 91/06287).
7. Bichon et al. teach compositions comprising microparticles filled with air or gas for use in ultrasonic echography (col. 1, lines 1-15; claims 1-3). Bichon et al. teach that the microparticle compositions can be prepared in aqueous solutions or in the solid form (i.e., the isolated cake or powder) for use in echography (col. 1, lines 1-8). Bichon et al. teach that the art recognizes that microparticles used for echography should have diameters in the range of about 0.5 to 10 micrometers (col. 2, lines 26-46). Bichon et al. exemplify a range of polymers useful for forming the membrane coat of the microparticles, including biodegradable polymers such as polylactides, and proteins such as albumin (col. 9, line 2-col. 10, line 8; claim 6). Bichon et al. teach that cross-linking proteins, such as albumin, with glutaraldehyde is an art-recognized method of forming microparticle membrane shells (col. 3, lines 20-53). Bichon et al. teach that the inclusion of sugars, such as sucrose, in order to stabilize the microparticles is known (col. 2, lines 8-46; col. 8, lines 20-30; col. 10, line 54-col. 11, line 4). Bichon et al. teach the inclusion of surfactants to increase membrane elasticity (claim 11; col. 2, lines 31-46; col. 10, lines 34-46). Bichon et al. also teach the inclusion of "polyethylene glycol of

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moderate to low  $M_w$ " (e.g. PEG 2000)) as membrane-plasticizing agents (col. 10, lines 44-46).

8. Bichon et al. do not explicitly teach the use of nitrogen as the gas within the core. Bichon et al. do not teach a microparticle with a membrane comprised of two layers of the polymers. Bichon et al. do not exemplify PEG 3350 as a preferred medium molecular weight polyethylene glycol.

9. Hilmann et al. teach that nitrogen is a preferred gas for incorporation into microparticles for use in echography (claim 14).

10. Bernstein et al. teach the layering of polymers to form microparticles of various size, durability, and release properties. Bernstein et al. teach that the microspheres can have layers containing different properties (p. 7, first full paragraph). Bernstein et al. teach that the same polymers and proteins exemplified by Bichon et al. can be layered to form multilayer microparticles (pp. 13-15). Bernstein et al. teach that amino acids are one type of agent than can be included in the microparticles (p. 5, last paragraph).

11. It would have been obvious to the person of ordinary skill in the art at the time of invention to produce a multilayer microparticle comprising the polymers of Bichon et al., to fill the core of the microparticles with nitrogen, and to add polyethylene glycol 3350 to the composition to arrive at the instantly claimed compositions.

12. The person of ordinary skill in the art would have been motivated to layer the polymers of Bichon et al. because Bernstein et al. teach that by layering the polymers, the size, durability, and release properties of microspheres can be modulated. The person of ordinary skill in the art would have expected success because Bernstein et al.

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teach that the same polymers exemplified by Bichon et al. can be layered in the preparation of the microparticles.

13. The person of ordinary skill in the art would have been motivated to use nitrogen as the gas in the core of the particles with a reasonable expectation of success because Bichon et al. and Berstein et al. teach that the microparticles can be used in echography when a gas is incorporated into the microparticles, and Hilmann et al. teach that nitrogen is a preferred gas for inclusion in microparticles used for echography.

14. The person of ordinary skill in the art would have been motivated to use polyethylene glycol 3350 in the formulations with a reasonable expectation of success because Bichon et al. teach the inclusion of moderate molecular weight polyethylene glycol, which encompasses polyethylene glycol 3350. Further, polyethylene glycol is substantially similar to the exemplified PEG 2000.

### ***Double Patenting***

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

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be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 1-14 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16, 19, 20, and 25-41 of U.S. Patent No. US 6,193,951. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to the same microparticles. '951 issued from US Patent Application 09/070,474. A restriction requirement was issued in '474 between microparticles containing a therapeutic drug and microparticles without a therapeutic drug. Applicant elected to prosecute the claims drawn to microparticles without a therapeutic drug in the response filed on October 4, 1999. The claims drawn to the elected invention issued as '951. Those claims are drawn to the same microparticles as are instantly claimed. Specifically, '951 teaches a bilayer microparticle comprising the herein-claimed polymers, and compositions comprising the microparticles and the herein-claimed excipients (claims 1, 4, 19, 20, 25-27, and 29). The claims of '951 are silent with respect to the sugar, which is present in the instant claims. However, the sugar of the instant compositions is not a therapeutic drug and the instant claims are not directed to the non-elected invention of '474. Specifically, see col. 5, lines 36-47 wherein sugars, including sucrose, are taught to be preferred in the microparticle compositions as bulking agents. The claims of '951 are also silent with respect to the incorporation of glycine and polyethylene glycol 3350. However, again the specification exemplifies incorporation of these agents as additives or excipients,

not therapeutic drugs (Example 11). Thus, the instant claims are directed to the elected invention of '474 and they are properly rejected over '951.

17. Claims 1-14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-27 of copending Application No. 10/977,100. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '100 are within the scope of the instant claims and thus anticipate the instantly claimed invention. Specifically, '100 teaches compositions comprising microparticles and the herein-claimed excipients (glycine, polyethylene glycol 3350, poloxomer, etc.). '100 teaches that the microparticles are comprised of two layers, said layers being comprised of the herein-claimed biodegradable polymers (polylactide) and glutaraldehyde cross-linked albumin. '100 teaches that the microparticles have a hollow core filled with nitrogen. The amounts of the components are more explicitly defined in '100 and the scope is thus narrower than for the instantly claimed compositions. Therefore, '100 anticipates the instantly claimed compositions.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. Claims 1-14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3, 16-24, and 28-



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37 of copending Application No. 09/637,516 in view of Bichon et al. (Applicant-cited reference on IDS: EP 0 458 745).

19. '516 teaches compositions comprising microparticles and the herein-claimed excipients (glycine, poloxomer, sucrose, polyethylene glycol, etc.). '516 teaches that the microparticles are comprised of two layers, said layers being comprised of the herein-claimed biodegradable polymers (polylactide) and glutaraldehyde cross-linked albumin. '516 teaches that the microparticles have a hollow core filled with nitrogen.

'516 teaches that the particles have diameters of about 100 to 800 nanometers.

20. '516 does not teach the microparticles as having the herein-claimed diameters of 1-10 micrometers.

21. Bichon et al., as discussed above, teach that microparticles having shells comprising the herein-claimed polymers, diameters of about 0.5 to about 10 micrometers, and cores filled with gas or air are useful for echography.

22. It would have been obvious to the person of ordinary skill in the art to adjust the diameter of the microparticles through routine experimentation and optimization to arrive at the microparticles of the instant invention.

23. The person of ordinary skill in the art would have been motivated to adjust the diameter of the microparticles of '516 to the herein-claimed range because Bichon et al. teach that microparticles comprised of the elements of '516 with diameters in the herein-claimed range are useful in echography. The person of ordinary skill in the art would have expected success because Bichon et al. teach that the production of

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microparticles comprised of the herein-claimed polymers with the herein-claimed diameters is a matter of routine experimentation for the ordinary skilled artisan.

This is a provisional obviousness-type double patenting rejection.

### ***Conclusion***

24. No claims are allowed.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin Capps whose telephone number is (571) 272-8646. The examiner can normally be reached on Monday-Friday, 7:30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

KC



**SREENI PADMANABHAN**  
**SUPERVISORY PATENT EXAMINER**